Arrhythmia genes more common than previously thought

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By sequencing known genes associated with cardiac arrhythmia risk in more than 20,000 people without an indication for genetic testing, scientists were able to identify pathogenic and likely pathogenic variants in nearly one percent of individuals, according to a study published in *Circulation*.

This rate is higher than those previously reported, according to Carlos G. Vanoye, Ph.D., research associate professor of Pharmacology and a co-author of the study.

"This study suggests the prevalence of genetic susceptibility to cardiac arrhythmia may be underestimated," Vanoye said.

The American College of Genetics and Genomics (ACMG) currently recommends that incidentally discovered pathogenic or likely pathogenic variants in 73 Mendelian disease genes be reported back to patients. This includes many genetic variants associated with congenital cardiac arrythmias, causing irregular heartbeats which can lead to stroke or sudden cardiac death.

However, many genetic variants in these known arrhythmia genes are of uncertain pathogenicity, and the approaches for classification of these variants is still in its clinical infancy.

"A person can carry a disease-causing gene variant but exhibit no obvious signs or symptoms of the disease," Vanoye said. "Because the genes we studied are associated with sudden death, which may have no

warning signs, discovery of a potentially life-threatening arrhythmia gene variant can prompt additional clinical work-up to determine risks and guide preventive therapies."

The current study used data from the Electronic Medical Records and Genomics sequencing (eMERGEIII) study. The eMERGEIII study investigated the feasibility of population genomic screening by sequencing 109 genes implicated across the spectrum of Mendelian diseases—inherited genetic diseases that are caused by a mutation in a single gene—in over 20,000 individuals, returning variant results to the participants, and using Electronic Health Record (EHR) and follow-up clinical data to ascertain patient phenotypes.

In the current study, investigators analyzed 10 arrhythmia-associated genes in individuals without an indication for genetic testing. They found 0.6 percent of study participants had genetic variants previously classified as pathogenic or likely pathogenic and several variants of uncertain significance.

The scientists determined the functional consequences of these variants of uncertain significance and used the data to refine the assessment of pathogenicity. In the end, they reclassified 11 of these variants: three that were likely benign and eight that were likely pathogenic.

In all, 0.6 percent of the studied population had a variant that increases risk for potentially life-threatening arrhythmia and there was overrepresentation of arrhythmia phenotypes among these patients, according to an analysis of electronic health records. This is a rate higher than previously known for genetic arrhythmia syndromes (approximately 1 in 2,000) and illustrates the potential for population genomic screening, Vanoye said.

"Population genomic screening can positively affect public health. Many

rare, disease-associated variants can be found this way which can then help determine the disease-risk of the carriers of these variants," Vanoye said. "Although the costs of genomic screening may be currently high, assessing patient risk followed up by clinical care would reduce the financial and emotional cost of the disease."

More information: Andrew M Glazer et al, Arrhythmia Variant Associations and Reclassifications in the eMERGE-III Sequencing Study, *Circulation* (2021). DOI: 10.1161/CIRCULATIONAHA.121.055562

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